論　文　目　録

報告番号	乙　医　第　1448 号	氏　名	西　角　　智　子

論　文

題目

PREVENTION OF POSTTRANSFUSION HEPATITIS BY SCREENING WITH SECOND-GENERATION ANTI-HCV ANTIBODY AND CLINICAL FEATURES OF HCV INFECTION

（供血者血のHCV第二世代抗体スクリーニングによる輸血後肝炎予防効果とHCV感染状況）

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平成8年6月25日発行
The Tokushima Journal of Experimental Medicine
第43巻　第1～2号　25～37ページに発表済

参考論文

1. Epidemiological characteristics of the incidence of hepatitis C virus (C100-3) antibodies in patients with liver diseases in the Inshore Area of the Yangtze River

（揚子江下流における肝疾患患者のC型肝炎ウイルス(C100-3)抗体の発症率の疫学的特徴）

平成5年3, 4月発行　Journal of Gastroenterology and Hepatology
第8巻　第2号　232～237ページに発表済

2. 輸血用血液におけるHCV(C100-3)抗体スクリーニングの効果
－第二世代検査法とHCV-RNA測定による評価－

平成5年10月25日発行　日本輸血学会雑誌
第39巻　第5号　853～859ページに発表済

3. HCV infection and its clinical features in recipients of blood screened for HCV(C100-3) antibody

（HCV(C100-3)抗体でスクリーニングした血液の受血者のHCV感染と臨床像）

平成6年1, 2月発行　Journal of Gastroenterology and Hepatology
第9巻　第1号　19～25ページに発表済

4. Incidence of hepatitis C virus (HCV) antibodies and HCV-RNA in blood donors and patients with liver diseases in the Inshore Area of the Yangtze River

（揚子江下流における供血者血および肝疾患患者血のC型肝炎ウイルス抗体とHCV-RNAの発症率）

平成6年5, 6月発行　Journal of Gastroenterology and Hepatology
第9巻　第3号　245～249ページに発表済

5. Prevalence of HCV-antibodies and HCV-RNA in donor blood in Tokushima prefecture

（徳島県における供血者のHCV抗体とHCV-RNAの罹患率）

平成6年6月25日発行
The Tokushima Journal of Experimental Medicine
第41巻　第1～2号　9～15ページに発表済

6. 輸血後肝炎におけるHCV抗体陰性例の実態

平成7年12月28日発行　消化器科
第21巻　第6号　534～540ページに発表済

7. Mutations in a hydrophilic part of the core gene of hepatitis C virus in patients with hepatocellular carcinoma in China

（中国における肝細胞癌患者のC型肝炎ウイルスのコア領域の親水性部分の変異）

平成9年2月発行　Journal of Gastroenterology
第32巻　第1号　47～55ページに発表済

2

西角智子　論文内容要旨

題　目

PREVENTION OF POSTTRANSFUSION HEPATITIS BY SCREENING WITH SECOND-GENERATION ANTI-HCV ANTIBODY AND CLINICAL FEATURES OF HCV INFECTION

（供血者血のHCV第二世代抗体スクリーニングによる輸血後肝炎予防効果とHCV感染状況）

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平成8年6月25日発行　The Tokushima Journal of Experimental Medicine
第43巻　第1～2号　25～37ページに発表済

内容要旨

本邦では，輸血後非A非B型肝炎（輸血後肝炎）予防のため1989年11月より全国日本赤十字社血液センターにおいて供血者血のC100-3抗体スクリーニングが開始された．その結果，10～20%に認められていた輸血後肝炎が，3%前後に低下したが，C100-3抗体のスクリーニングだけでは輸血後肝炎を予防するのは不十分であった．1992年2月より輸血血のC型肝炎ウイルス(HCV)スクリーニングに第二世代抗体が導入されるようになり，輸血後肝炎の発生率はさらに低下したが，未だ数%の発生が認められる．しかし，これらの輸血後肝炎がHCV感染によるものかどうかは明らかにされていない．そこで著者らは，第二世代抗体スクリーニング後の輸血後肝炎発生率とHCV感染状況を明かにするため，第二世代抗体陰性血輸血例について，ALT，第二世代抗体，および適宜HCV-RNAを測定し，C100-3抗体スクリーニング時の輸血後肝炎と比較検討した．さらに，輸血後肝炎の病態を明らかにするため，ALT値の推移とHCV-RNA陰陽別の手術条件についても検討した．

対象は1992年2月（第二世代抗体スクリーニング）以後の輸血例205例のうちの経時的に観察し得た115例(A)および1989年6月から1992年1月の間のC100-3抗体スクリーニングの輸血例209例のうち，retrospectiveに輸血血が同定され，第二世代抗体陰性血が輸血された輸血例93例(B)を用いた．輸血例(A)および(B)について輸血前，輸血後1，2，3，4，6，8,12,24，36，48週の一般肝機能検査，輸血後12，24週の第二世代抗体およびHCV-RNAを測定し，輸血後肝炎の発生率とHCVの感染状況を検討した．HCV-RNAは輸血後肝炎確診例3例，疑診例8例の輸血血，患者血について測定した．輸血後肝炎11例について手術時間，麻酔時間，出血量，血圧等の手術条件を検討した．

輸血後肝炎の診断は1992年3月の厚生省肝炎研究連絡協議会による輸血後非A非B型肝炎診断基準に従い，輸血後肝炎例について，ALTの異常値（30 IU/L以上）が輸血後6か月以上確認できたものを慢性化(+)とした．

得られた結果は次の如くである．

1. 第二世代抗体陰性血輸血例208例の輸血後肝炎（確診および疑診例）発生率は11例(5.2%)であり，C100-3抗体スクリーニング時の10.5%に比較し有意に減少した．
2. 輸血後肝炎11例におけるHCV-RNA陰陽別のALT活性の経過は，HCV-RNA陽性例ではALT値ピークまでの期間が長く，4週以後の第二ピークが存在する率が高く，陰性例ではALT値ピークまでの期間が短く，4週以内の一過性の上昇がみられた．
3. HCV陰陽別手術条件を比較すると明きらかな差異はみられなかったが，確診例では疑診例に比べて手術時間および麻酔時間が長く，出血量が多い傾向がみられた．
4. 輸血後肝炎の診断にALT値のみならず，手術条件の影響も考慮する必要があると考えられた．
5. ALT値の4週以後の第二ピークおよびHCV-RNA陽性で輸血後肝炎と考えられた例が11例中2例にみられたが，いずれもretrospectiveに第二世代陰性血輸血例であった．
6. HCV-RNAおよび第二世代抗体が陰性で，ALT値が4週以内の一過性の上昇を示し，輸血後肝炎と診断された例が11例中5例にみられた．
7. 現行の輸血後肝炎診断基準はALT値に基づくもので輸血後肝炎の診断には不十分であり，新しい診断基準の導入が必要と考えられた．

(3)

PREVENTION OF POSTTRANSFUSION HEPATITIS BY SCREENING WITH SECOND-GENERATION ANTI-HCV ANTIBODY AND CLINICAL FEATURES OF HCV INFECTION

By

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Reprinted from
The Tokushima Journal of Experimental Medicine
Vol. 43, No. 1~2

June, 1996

Tokushima J. exp. Med. 43, 25~37, 1995

PREVENTION OF POSTTRANSFUSION HEPATITIS BY SCREENING WITH SECOND-GENERATION ANTI-HCV ANTIBODY AND CLINICAL FEATURES OF HCV INFECTION

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(Accepted: March 25, 1996)

After adaptation of the second-generation anti-hepatitis C virus (HCV) test, the incidence of post-transfusion hepatitis (PTH) resulted in 5.2% (11/208), which was significantly lower than that 10.5% (22/209) demonstrated by screening donor blood for C100–3 antibody.

The 11 cases of PTH, three were classified as definite PTH and the other were as suspected one. Of two cases with definite PTH and two cases with suspected PTH, their blood samples after transfusion became positive for HCV-RNA, and three cases of those showed a second peak of alanine aminotransferase (ALT) more than 4 weeks after operation. On the other hand, of seven cases containing one definite PTH, their blood samples after transfusion became negative for HCV-RNA, and five cases of those showed ALT peaks within 4 weeks after operation, and returned to normal levels of ALT thereafter.

Moreover, in cases of definite PTH, the periods of surgery and anesthesia were longer and the volume of bleeding was much more during operation than in cases of suspected PTH, although the differences were not statistically significant.

These findings suggested that cases of PTH include those of transient liver disease attributable to surgery as well as those of HCV infection.

In 11 cases of PTH, we consider that 2 cases is true PTH, because these are HCV-RNA positive and have second peak more than 4 weeks after operation and 5 cases is questionable by clinical date.

Thus new diagnostic criteria should have established.

Key words: Posttransfusion hepatitis — Second-generation anti-HCV antibody — HCV-RNA — Screening test

In 1989, Chiron, a US company, succeeded in cloning a part of the gene for the hepatitis C virus (HCV)[2] and reported a method for measuring HCV antibody (C100–3)[9]. Since then, a number of assays using HCV-related antibodies[13] and methods of measuring HCV-RNA[14] have been developed. Studies using these methods have revealed that many cases of hepatitis which had previously been regarded as being non-A, non-B hepatitis, were actually cases of hepatitis C[1]. In Japan, the Japan Red-Cross Blood Centers throughout the country began, in November 1989, to screen donor blood for the C100–3 antibody to prevent post-transfusion non-A, non-B hepatitis (PTH). As a result, the incidence of PTH decreased to about 3% from its previous level of 10–20%[7,8]. However, even when C100–3 antibody negative blood was used for transfusion, hepatitis C still developed in a small percentage of

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blood recipients[5]. This indicates that HCV infection via blood transfusion cannot be adequately prevented solely by screening for the C100–3 antibody. The first generation anti-HCV antibody (C100–3) is an antibody specific to the protein produced from the NS 4 region (non-structural region) of the HCV genome. In 1990, a second-generation anti-HCV antibody was developed. This antibody contains antibodies specific to the proteins produced from NS3, NS4 regions (non-structural region) of the HCV genome and the recombinant HCV antigen (core region)[12]. The second-generation antibody is expected to elevate the HCV detection rate compared to C100–3 antibody[4,10]. In Japan, this new antibody has been used to check donor blood since February 1992, on the basis of an expectation that its use will further reduce the incidence of PTH. Because only a short period has passed since the beginning of use of this new antibody, few reports have been published concerning the incidences of hepatitis and HCV infection in individuals who received blood checked using this new antibody. The present study was undertaken to examine the incidences of such hepatitis and HCV infection in patients who received blood with the second-generation antibody for negative. And individuals who had been transfused with the second-generation antibody negative blood were subjected to the following tests: <1> alanine aminotransferase (ALT), <2> second-generation antibody, and <3> HCV-RNA. The results of these tests were compared to those obtained from patients who had developed hepatitis after transfusion of blood screened for HCV C100–3 antibody. Furthermore, in cases where the donor blood, which had been screened for C100–3 antibody, could be later found the second-generation antibody negative, we analyzed the incidence of HCV infection after transfusion.

Subjects and Methods

1. Subjects

1) Patients after transfusion

From January 31, 1992, when screening of blood using the second-generation antibody was started at the Japan Red-Cross Blood Centers, 205 patients received transfusion with the second generation antibody negative blood at our hospital or its related facilities. Of these patients, 115 could be followed after transfusion, and were included in this study (Group A). Between June 1989 and January 1992, 209 patients[6] who received C100–3 antibody negative blood at our hospital or its related facilities were employed as the control. In 93 of these 209 patients, donor blood was measured retrospectively, and later found to be second-generation antibody negative. These 93 patients were also included in this study (Group B). The following patients were excluded; <1> children, <2> patients who received 20 units or more of blood, <3> patients with a history of liver disease, <4> patients with liver injury, <5> patients who were either HBs antigen or second-generation antibody positive, and <6> patients who could not be followed for 6 months after transfusion.

2) Transfusion blood

The following blood samples were examined: (1) the donor blood (16 units) used for transfusion to each of the Group A patients who were diagnosed with having PTH, and (2) the donor blood (288 units) used for transfusion to each of the Group B patients, which was retrospectively found to be second-generation antibody negative.

3) Blood from transfused patients

Blood was sampled from each patient at a point before transfusion, every week during the first month after transfusion and every 2 weeks during the second and third month after transfusion. If possible, blood sampling was continued until one year after transfusion. All blood samples were stored, frozen at −20°C, until use.

2. Methods

In both Group A and Group B, ALT were carried out before and 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 weeks after transusion. Second-generation antibody and HCV-RNA were examined 12 and 24 weeks after transfusion. Based on these data, the incidences of PTH and clinical features of HCV infection were examined. HCV-RNA was measured in 3 patients who were definite PTH and 8 patients who were suspected PTH. Patients in whom abnormal ALT (over 30 IU/L) was confirmed when followed for more than 6 months after transfusion were rated as having chronic hepatitis.

3. Assays

Second-generation antibody assay was carried out using an Abbot kit (PHA method). HCV-RNA was quantified using the nested PCR method of Okamoto et al.[14], with the 5'-non-coding region serving as a primer.

4. Criteria for diagnosis of PTH

The diagnosis of PTH was based on the criteria for the diagnosis of post-transfusion non-A, non-B hepatitis prepared in March 1992 by Liaison Conference for the Study of Hepatitis of Japan.

5. Evaluation of effect of screening for HCV antibody in prevention of PTH

The effects of second-generation antibody screening in preventing PTH was assessed by comparing the incidence of PTH between control[6].

6. Operative condition of patients with PTH

In PTH, the operation time, the duration of anesthesia, the volume of blood lost during operation, pre-operation blood pressure and minimum blood pressure during operation were measured.

7. Statistical analysis

The incidences of PTH were tested using the Chi-squared test. Averages were tested using Student's t-test. $P<0.05$ was regarded statistically significant. Probabilities were using Fisher's exact approximation.

Results

1. Incidence of PTH

Table 1 shows the incidence of PTH in recipients transfused with second-generation

Table 1.
Inscidence of PTH in recipients with transfused second generation antibody negative bloods

Recipients	No	Screening test	period	Inscidence of PTH (%)		
A	115	2nd	1992.2~1993.6	Defined	1(0.9%)	
				Suspected	3(2.6%)	
				Defined+Suspected	4(3.5%)	
B	93	C100–3	1989.6~1992.1	Defined	2(2.2%)	
				Suspected	5(5.4%)	
				Defined+Suspected	7(7.6%)	☆
Total	208		1989.6~1992.12	Defined	3(1.4%)	
				Suspected	8(3.8%)	
				Defined+Suspected	11(5.2%)	
Control[6]	209	C100–3	1969.6~1992.1	Defined	7(3.3%)	☆
				Suspected	15(7.2%)	
				Defined+Suspected	22(10.5%)	

PTH: post-transfusion hepatitis, ☆: $P<0.05$

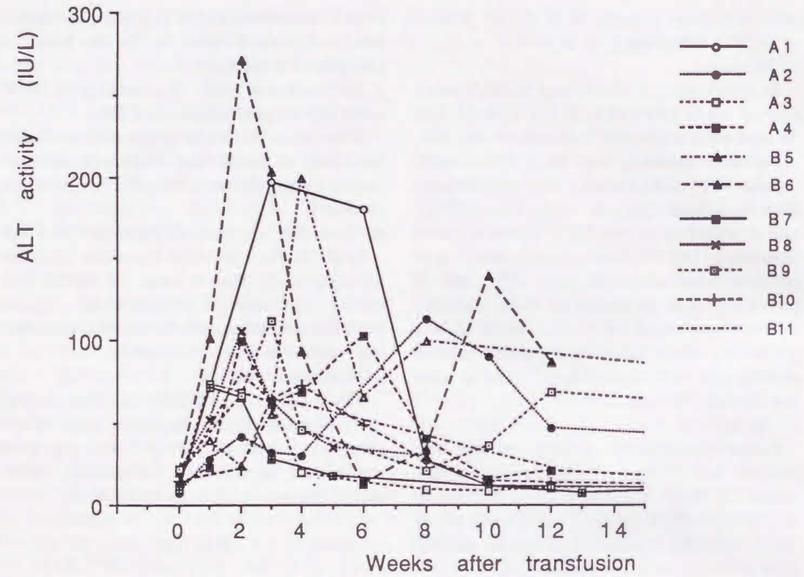

Fig. 1. Changes of alanine aminotransferase (ALT) activity of posttransfusion hepatitis (PTH)
The pattern of changes in ALT activity was variable.

antibody negative bloods. In Group A (n=115), one patient (0.9%) was definite PTH and 3 patients (2.6%) were suspected PTH. In Group B (n=93), 2 patients (2.2%) were definite PTH and 5 patients (5.4%) were suspected PTH. Totally, from the two groups, 3 patients (1.4%) were definite PTH and 8 patients (3.8%) were suspected PTH. The incidences of definite PTH and suspected PTH after C100–3 antibody screening have been reported as 3.3% and 7.2%, respectively[6]. Thus, both the incidence of definite PTH and that of suspected PTH were lower after second-generation antibody screening than after C100–3 antibody screening, although the differences were not statistically significant. However, when definite PTH and suspected PTH are combined, the incidences of PTH in Group A (3.5%, 4 cases), Group B (7.6%, 7 cases) and the total subjects of this study (5.2%, 11 cases) were significantly lower than the incidence of PTH (10.5%, 22 cases) after C100–3 antibody screening.

2. Changes in ALT activity in 11 patients with PTH

Fig. 1 shows the time course of ALT activity in 11 patients who were definite PTH and suspected PTH following transfusion of second-generation antibody negative blood. The pattern of changes in ALT activity was variable. In some cases, the activity reached a peak within 4 weeks after transfusion. In other cases, it reached a peaak after the fourth week. Furthermore, in some cases, two or more peaks of ALT activity were present.

Fig. 2 shows the time course of ALT

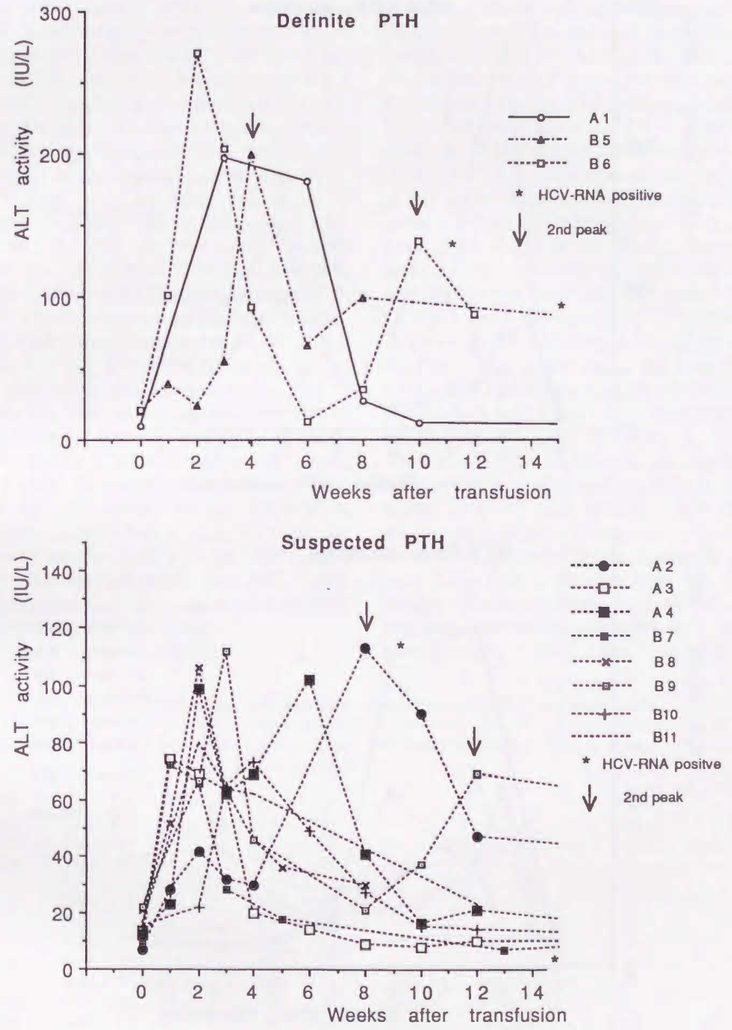

Fig. 2. Changes of ALT activity in patients with definite and suspected PTH
In the 3 definite PTH, two (B5 and B6) showed a second peak of ALT activity (↓) after the 4th week. These 2 cases were HCV-RNA positive. In the suspected PTH, two (A2 and B9) showed a second peak of ALT activity (↓) after the 4th week. A2 and B7 were RNA positive.

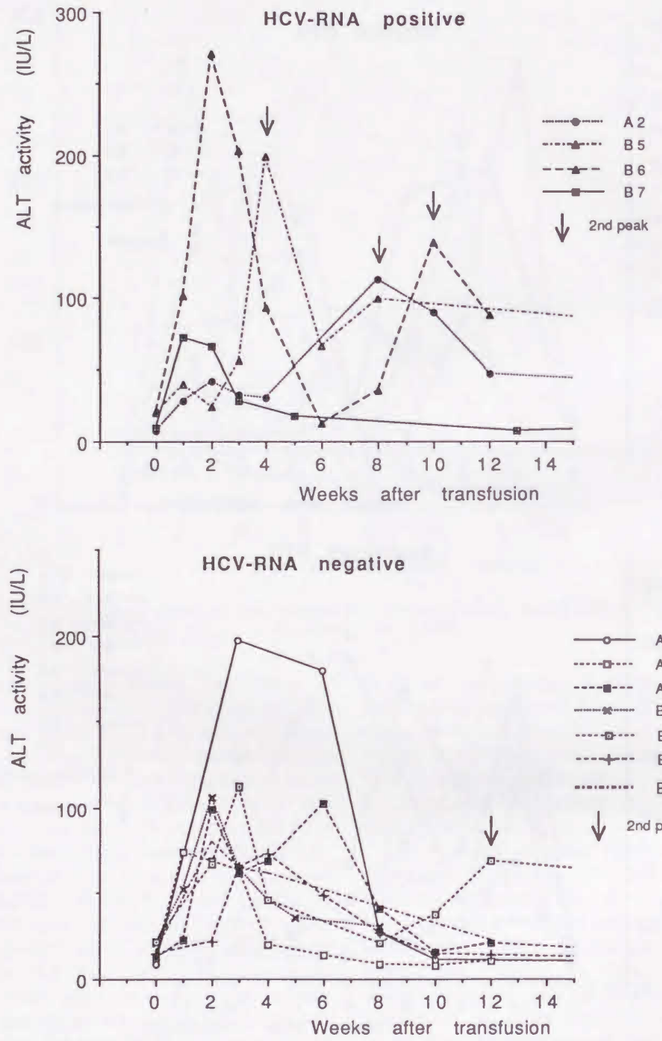

Fig. 3. Changes of ALT activity in patients with HCV-RNA positive and negative
In the 4 HCV-RNA positive cases, three (A2, B5 and B6) had a second peak after the 4th week. In the HCV-RNA negative cases, one (B9) had a second peak after the 4th week.

activity for definite PTH and suspected PTH, in relationship to the results of HCV-RNA positive conversion(*). In the 3 definite PTH, one (A1) showed a peak ALT activity 3 weeks after transfusion. In this cases, the ALT activity decreased gradually from the third week on and was normal from the 10th week on. This cases was HCV-RNA negative. The other two cases of definite PTH showed a second peak of ALT activity (↓) after the 4th week. These 2 cases were HCV-RNA positive conversion. In the suspected PTH, some had a peak of ALT activity within 4 weeks after transfusion, while others had a second peak after 4 weeks (↓; A2, B9). Of these cases, A2 and B7 were RNA positive conversion. Fig. 3 shows the time course of ALT activity in relation to the positive or negative of HCV-RNA. In the 4 HCV-RNA positive cases, three (A2, B5 and B6) had a second peak after the 4th week. In the HCV-RNA negative cases, 5 had a peak ALT activity within 4 weeks, and 2 (A4 and B10) had a peak after the 4th week. One HCV-RNA negative cases had the second peak of ALT activity after the 4th week.

3. Clinical features of PTH

Table 2 shows the following parameters for Groups A and B: age, sex, units of blood transfused, levels of ALT peak, time from transfusion to ALT peak, the existence of the second peak of ALT activity, response to second-generation anti-HCV antibody, existence of HCV-RNA in blood, existence of HCV-RNA in donor blood and existence of chronic hepatitis. In Group A, one case of definite PTH (A1) had neither the second peak of ALT activity nor chronic hepatitis. Both second-generation anti-HCV antibody and HCV-RNA were negative in this case. Of the 3 cases of suspected PTH in Group A, one case (A2) showed a second peak of ALT activity. In this case, the time from transfusion to the first peak of ALT activity was 56 days, which was longer than the time for the other 3 cases in Group A. HCV-RNA was positive in this case. In Group B, both of the 2 cases of definite PTH had the second peak of ALT activity. HCV-RNA was positive in both of these cases. Of the 5 cases of suspected PTH in Group B, one case (B9) had a second peak of ALT activity. The donor blood used for this case was also HCV-RNA positive. HCV-RNA was positive in blood from each of the 4

Table 2. Clinical and serological data of recipients with PTH and their donor

Recip. No	PTH	Age	Sex	Unit	ALT (IU/L)	Time (days)	2nd Peak	2nd HCV_R	RNA_{-R}	RNA_{-D}	Chronisity
A1	Defin	68	M	4	197	21	−	−	−	−	−
A2	Susp	39	F	5	113	56	+	−	+	NT	−
A3	Susp	67	F	5	74	7	−	−	−	−	−
A4	Susp	59	M	2	102	42	−	−	−	−	−
B5	Defin	65	M	2	199	28	+	−	+	+	+
B6	Defin	70	M	3	271	14	+	−	+	+	−
B7	Susp	75	M	1	72	7	−	−	+	−	−
B8	Susp	57	F	2	106	14	−	−	−	−	−
B9	Susp	72	M	2	112	21	+	−	−	+	−
B10	Susp	72	M	3	73	28	−	−	−	+	−
B11	Susp	48	F	4	80	14	−	−	−	NT	NT

PTH: post-transfusion hepatitis, Recip: recipients, ALT: peak level of ALT, Time: time until the ALT peak, 2nd peak: existence of 2nd peak, 2nd HCV_R: 2nd generation HCV-Ab of recipient blood, RNA_{-R}: RNA of recipient blood, RNA_D: RNA of donor blood, Defin: definite case, Susp: suspected case, NT: not tested.

Table 3. Clinical and serological data of recipients with definite and suspected PTH

Recipients No	PTH	Age	Sex	Unit	peak ALT (IU/L)	Time to peak (days)	Existence of 2nd peak
A1	Defin	68	M	4	197	21	−
B5	Defin	65	M	2	199	28	+
B6	Defin	70	M	3	271	14	+
Mean±S.D.		67.7±2.5		3.0±1.0	222.3±42.2	21.0±7.0	2/3(66.7%)
A2	Susp	39	F	5	113	56	+
A3	Susp	67	F	5	74	7	−
A4	Susp	59	M	2	102	42	−
B7	Susp	75	M	1	72	7	−
B8	Susp	57	F	2	106	14	−
B9	Susp	72	M	2	112	21	+
B10	Susp	72	M	3	73	28	−
B11	Susp	48	F	4	80	14	−
Mean±S.D.		61.1±12.8		3.0±1.5	91.5±18.4	23.6±17.5	2/8(25.0%)
p value		NS		NS	p<0.0001	NS	NS

PTH: post-transfusion hepatitis, Peak ALT: peak level ALT, Time to peak: time until the ALT peak, Defin: definite case, Susp: suspected case.

patients who had a second peak of ALT activity. The donors, whose blood was transfused to these 4 patients, were also HCV-RNA positive. Second-generation antibody was negative in all of these 4 patients and donors. Hepatitis followed a chronic course in only one(B5) of these 11 patients. HCV-RNA was positive in the blood in this case and also in the blood of the donor used for transfusion. This patient also had a second peak of ALT activity.

Table 3 shows the age, sex, units of transfused blood, levels of ALT peak, time from transfusion to peak of ALT activity, and the existence of the second peak of ALT activity in patients with definite and suspected PTH. The average of peak of ALT activity was significantly higher in the definite group (222.3 IU/L) than in the suspected group (91.5 IU/L). The second peak of ALT activity was seen in 2 (66.7%) of the 3 cases in the definite group and 2 (25.0%) of the 8 cases in the suspected group. The percentage of cases showing the second peak of ALT activity tended to be higher in the definite group than in the suspected group, although this difference was not statistically significant. Table 4 shows the age, sex, units of transfused blood, peak level of ALT activity, time from transfusion to ALT peak and the existence of the second peak of ALT activity for the HCV-RNA positive patients with PTH and the HCV-RNA negative patients with PTH. The peak level of ALT activity tended to be higher in the HCV-RNA positive group (163.8IU/L) than in the HCV-RNA negative group (106.3IU/L). The time from transfusion to ALT peak did not differ markedly between the two groups. The percentage of cases showing a second peak of ALT activity was higher in the HCV-RNA positive (75%, 3/4) than in the HCV-RNA negative group (14.3%, 1/7), although this difference was not statistically significant.

4. Operative condition of patients with PTH

Table 5 shows the condition of the surgery carried out on each of the cases of definite

Table 4. Clinical and serological data of recipients with HCV-RNA positive and negative

HCV-RNA	No	PTH	Age	Sex	Unit	peak ALT (IU/L)	Time to peak (days)	Existence of 2nd peak
+	A2	Susp	39	F	5	113	56	+
+	B5	defin	65	M	2	199	28	+
+	B6	defin	70	M	3	271	14	+
+	B7	Susp	75	M	1	72	7	+
	Mean±S.D.		62.3±16.0		2.8±1.7	163.8±89.0	26.3±21.7	3/4(75.0%)
−	A1	Defin	68	M	4	197	21	−
−	A3	Susp	67	F	5	74	7	−
−	A4	Susp	59	M	2	102	42	−
−	B8	Susp	57	F	2	106	14	−
−	B9	Susp	72	M	2	112	21	+
−	B10	Susp	72	M	3	73	28	−
−	B11	Susp	48	F	4	80	14	−
	Mean±S.D.		63.3±8.9		3.1±1.2	106.3±43.1	21.0±11.4	1/7(14.3%)
	p value		NS		NS	NS	NS	NS

Peak ALT: peak level of ALT, Time to peak: time until the ALT peak, Defin: definite case, Susp: suspected case, NS: not significant

Table 5. Operative condition of patients with defined and suspected PTH

PTH	No.	Time ope (min)	Time anes (min)	Bleeeding (ml)	Pre BP (mmHg)	Min BP (mmHg)	RNA
Defined	A 1	788	920	3020	120/ 70	85/60	−
Defined	B 5	230	300	940	130/ 76	83/46	+
Defined	B 6	1220	1290	1000	120/ 80	104/60	+
Mean±S.D.		746.0±496.3	836.7±500.2	1653.3±1184.0	123.3±5.8 75.3±5.0	90.7±11.6 55.3± 8.1	
Suspected	A 2	245	320	720	90/ 60	80/45	+
Suspected	A 3	455	530	2300	130/ 85	80/50	−
Suspected	A 4	381	625	1600	100/ 70	80/58	−
Suspected	B 7	275	260	500	165/100	62/35	+
Suspected	B 8	1070	1215	1200	110/ 70	86/44	−
Suspected	B 9	205	490	1000	150/ 80	90/50	−
Suspected	B10	350	470	1400	120/ 70	80/50	−
Suspected	B11	235	315	200	124/ 54	85/45	−
Mean±S.D.		402.0±282.8	528.1±303.9	1115.0±666.8	123.6±24.9 73.6±14.5	80.4±8.3 47.1±6.6	

PTH: post-transfusion hepatitis, Time ope: time of operation, Time anes: time of anesthesia, Pre BP: pre-operation blood pressure, Min BP: minimum blood pressure during operation.

Table 6. Operative condition of patients with HCV-RNA positive and negative

HCV-RNA	No.	Time ope (min)	Time anes (min)	Bleeeding (ml)	Pre BP (mmHg)	Min BP (mmHg)
+	2	245	320	720	90/ 60	80/45
+	5	230	300	940	130/ 76	83/46
+	6	1220	1290	1000	120/ 80	104/60
+	7	275	260	500	165/100	62/35
Mean±S.D.		492.5±485.4	542.5±499.0	790.0±227.7	126.3±30.9 79.0±16.5	82.3±17.2 46.5±10.3
−	1	788	920	3020	120/ 70	85/60
−	3	455	530	2300	130/ 85	80/50
−	4	381	625	1600	100/ 70	80/58
−	8	1070	1215	1200	110/ 70	86/44
−	9	205	490	1000	150/ 80	90/50
−	10	350	470	1400	120/ 70	80/50
−	11	235	315	200	124/ 54	85/45
Mean±S.D.		497.7±317.2	652.1±310.2	1531.4±912.3	122.0±15.7 71.3± 9.7	83.7±3.9 51.0±6.0

Time ope: time of operation, Time anes: time of anesthesia, Pre BP: pre-operation blood pressure, Min BP: minimum blood pressure during operation.

PTH and suspected PTH. The operation time, the duration of anesthesia and the volume of blood lost during surgery tended to be greater in the definite PTH than in the suspected PTH, although none of these differences were statistically significant. When these patients were divided into the HCV-RNA positive group and the HCV-RNA negative group (Table 6), the operation time and the duration of anesthesia did not differ between the two groups, while the volume of blood lost during surgery tended to be smaller in the HCV-RNA positive group than in the HCV-RNA negative group.

Discussion

After donor blood began to be checked using C100–3 antibody, non-A, non-B PTH decreased remarkably, but its incidence is still not equal to zero[6]. Second-generation antibody assay was then developed and it began to be used to check donor blood in February 1992. This is expected to further reduce the incidence of PTH. However, the effect of screening donor blood for the second-generation antibody in preventing PTH has not yet been established. The retrospective study by Karlsson et al.[11] demonstrated that all cases of PTH had received blood which had been C100–3 antibody negative, second-generation antibody positive and HCV-RNA positive. Their study suggested that screening donor blood for the second-generation antibody would reduced PTH-C. A prospective study concerning a check of donor blood using second-generation anti-HCV antibody revealed that PTH-C never developed after transfusion of second-generation antibody negative blood, and that one case of non-A, non-B, non-C hepatitis was seen after transfusion of second-generation antibody negative blood[3]. A retrospective study, however, showed that hepatitis C developed even after transfusion of second-generation antibody negative blood. In the present study,

the authors examined the incidences of PTH and HCV infection among recipients of blood screened for using the second-generation antibody. The subjects of this study were Group A as well as Group B. In Group A and Group B, 1.4% were definite PTH and 3.8% were suspected PTH. These incidences were lower than those for the individuals who received blood screened for C100–3 antibody (3.3% and 7.2%, respectively). However, when definite PTH and suspected PTH are totaled, the incidence of this condition was significantly lower in the individuals who received blood checked using the second-generation antibody (5.2%) than in the individuals who received blood screened for C100–3 antibody. When the clinical features of patients with PTH was followed, all cases were HCV antibody negative, but some cases were HCV-RNA positive. This suggests that some of these patients had been infected with HCV. However, PTH followed a chronic course in only one patient. Furthermore, HCV-RNA was positive in only 2 of the 3 definite PTH and 2 of the 7 suspected PTH. It is therefore doubtful that all 11 cases of PTH, diagnosed using conventional criteria, really had PTH. When the time course of ALT activity in these 11 cases was analyzed, various patterns of change were observed. In some cases, the activity reached a peak within 4 weeks after transfusion, while in others it reached a peak after the fourth week. The first peak was sometimes followed by a second peak. When patients definite PTH were compared with patients suspected PTH, no parameter other than ALT activity differed significantly between these two groups. Of the 3 HCV-RNA positive cases in the definite group, 2 showed a second peak of ALT activity after the 4th week, and all HCV-RNA negative cases in this group showed a temporary elevation in ALT activity within the first 4 weeks after transfusion. These results suggest that HCV infection is related to the time from transfusion to the peak of ALT activity or the existence of a second peak of ALT activity. Following this finding, we analyzed the time course of ALT activity in HCV-RNA positive cases and HCV-RNA negative cases. Although this analysis revealed no significant inter-group difference, we noted that 3 of the 4 HCV-RNA positive cases had a second peak of ALT activity after the 4th week. This suggests the ALT activity often rises 4 weeks or more after transfusion in cases of PTH-C. At the same time, however, one of the HCV-RNA negative cases suspected of having PTH also had a second peak of ALT activity (about 100 IU/l) after the 4th week. The donor blood was also HCV-RNA positve. It is unknown whether this case is a false positive case or a true positive case. In any event, this case needs to be followed. When conditions of surgery were compared between the definite group and the suspected group, the operation time, the duration of anesthesia and the volume of blood lost during surgery tended to be greater in the definite group than in the suspected group, althouh none of these differences were statistically significant. No parameter of surgery differed significantly between HCV-RNA positive patients and HCV-RNA negative patients. These results suggest that the current ALT based criteria for the diagnosis of PTH are affected more greatly by operative conditions than by HCV infection. In the present study, one patient, who was definite PTH according to the current criteria, showed only a temporary rise in ALT activity during the first 4 weeks after transfusion, without showing a second peak. It seems therefore probable that this is a false positive case. Since the operation time for this case was long and the volume of blood lost during surgery was great in this case, it seems more appropriate to regard this case as having temporary rise in ALT activity due to postoperative liver damage. It is therefore advisable that individuals who are HCV-RNA negative and

show only a temporary rise in ALT activity within 4 weeks after transfusion should be regarded as having postoperative liver damage, rather than they are definite PTH. In the present study, 2 cases (B5 and B6) had a second peak of ALT activity after they showed the first peak 4 weeks or more after transfusion. The blood samples of these 2 cases and the donors from whom they received blood were HCV-RNA positive. These 2 cases were therefore diagnosed as having PTH-C. In Case A2 (suspected PTH according to the current criteria), the blood of the donor whose blood had been transfused to this patient was HCV-RNA positive, and this patient had a second peak of ALT activity. This case is therefore highly likely to have developed PTH. In this case, however, 4 of the 5 units of donor blood were HCV-RNA negative, and the remaining unit could not be checked for HCV-RNA. In Cases B9 and B10, the donor blood was HCV-RNA positive. However, since the blood of these 2 cases was second-generation antibody negative and HCV-RNA negative, it is unlikely that PTH had developed in these cases. In Cases A3, A4, B8 and B11, both the blood samples of the donor and the recipient were second-generation antibody negative and HCV-RNA negative. ALT activity reached a peak 4 weeks or more after transfusion in all these cases but A4. Therefore, it seems likely that A3, B8 and B11 had postoperative liver damage rather than PTH. The number of blood recipients whose blood was found to be HCV-RNA positive after transfusion was 4. The clinical features of 2 (B5 and B6) of these 4 cases were identical to the pathophysiological features of PTH. Of the remaining 2 cases, one (B7) showed only slight temporary abnormalities of liver function within 4 weeks after transfusion. Because this case had not received a check of his own blood for HCV-RNA prior to transfusion, we cannot rule out that this case had already been HCV-RNA before transfusion. Of individual who received second-generation antibody negative blood, 2 cases were found to have HCV-RNA in their blood after transfusion and were definite PTH. Both cases were from Group B. Because the unused portion of donor blood was stored frozen for long periods of time, its check using the second-generation antibody involves a risk of false negative judgment. After screening donor blood for second-generation antibody was started, the incidence of PTH-C decreased to a very low level. Although some individuals who received transfusion of blood checked using this antibody were diagnosed as having PTH according to the current criteria, it is doubtful that the judgments for these cases are correct, because the change in ALT activity was temporary and seen within the first 4 weeks in some of these cases. It is now desirable to develop new criteria for the diagnosis of PTH which can cope with recent advances in testing methods.

Acknowledgments

The authors are indebted to the following facilities and their members for their cooperation with this study: Tokushima University Hospital Transfusion Department (Mr. Y. Kuroda, director, and Mr. H. Watanabe), Tokushima University Hospital Laboratory (Mr. K. Shima, director), Tokusima Prefecture Red Cross Blood Center (Mr. E. Endo, president, and Mr. F. Yokoishi), Anan Kyoei Hospital (Mr. T. Harada, president, and Mr. H. Inoue), Kensei Hospital (Mr. K. Kadota and Mr. K. Toibana) and several clinical department of Tokushima University Hospital. The authors' thanks are also addressed to their colleague at the Second Department of Internal Medicine of our university.

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4

論文審査の結果の要旨

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題目

PREVENTION OF POSTTRANSFUSION HEPATITIS BY SCREENING WITH SECOND-GENERATION ANTI-HCV ANTIBODY AND CLINICAL FEATURES OF HCV INFECTION

（供血者血のHCV第二世代抗体スクリーニングによる輸血後肝炎予防効果とHCV感染状況）

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平成8年6月25日発行 The Tokushima Journal of Experimental Medicine
第43巻 第1～2号 25～37ページに発表済

要旨

1989年より供血者血のC型肝炎ウイルス(HCV)（C100-3）抗体スクリーニングが開始された。次いで1992年より第二世代抗体検査が導入され、輸血後肝炎は激減したが未だ数%が認められる。しかし、これらの輸血後肝炎がHCV感染によるものかどうかは明らかにされていない。そこで著者らは、HCV抗体スクリーニング後の輸血後肝炎発生率とHCV感染状況について検討している。

対象は1992年2月（第二世代抗体スクリーニング）以後の輸血例205例のうち経時的に観察し得た115例(A群)および1989年6月から1992年1月の間（C100-3抗体スクリーニング）の輸血例209例のうち、第二世代抗体陰性血が輸血された輸血例93例(B群)を用いている。輸血例(A群)および(B群)について輸血前、輸血後1, 2, 3, 4, 6, 8, 12, 24, 36, 48週の肝機能検査、輸血後12, 24週の第二世代抗体およびHCV-RNAを測定し、HCV-RNAは輸血後肝炎確診例3例、疑診例8例の輸血血および患者血について測定している。輸血後肝炎11例について手術時間、麻酔時間、出血量、血圧等の手術条件を検討している。

得られた結果は次の如くである。

1. 第二世代抗体陰性血輸血例208例の輸血後肝炎発生率は11例(5.2%)であり、C100-3抗体スクリーニング時の10.5%に比較し有意に減少した。
2. 輸血後肝炎11例におけるHCV-RNA陰陽別のALT活性の経過は、HCV-RNA陽性例ではALT値ピークまでの期間が長く、4週以後の第二ピークが存在する率が高く、陰性例ではALT値ピークまでの期間が短く、4週以内の一過性の上昇がみられた。
3. HCV陰陽別手術条件を比較すると明らかな差異はみられなかったが、確診例では疑診例に比べて手術時間および麻酔時間が長く、出血量が多い傾向がみられ、輸血後肝炎の診断に手術の影響が考えられた。
4. HCV-RNAおよび第二世代抗体が陰性で、ALT値が4週以内の一過性の上昇を示し、輸血後肝炎と診断された例が11例中5例にみられた。
5. 現行の輸血後肝炎診断基準はALT値に基づくもので輸血後肝炎の診断には不十分であり、新しい診断基準の導入が必要と考えられた。

本研究は、HCV抗体スクリーニング後の輸血後肝炎の発生率とHCV感染状況を明らかにし、現行の輸血後肝炎の診断基準では不十分であることを指摘したもので、今後この方面の研究に寄与し得るものであり、学位授与に値すると判定された。